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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/041,977	01/09/2002	Charles A. Nicolette	GA0118USC	7476

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EXAMINER	
PONNALURI, PADMASHRI	

ART UNIT	PAPER NUMBER
1639	

DATE MAILED: 04/21/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/041,977	NICOLETTE, CHARLES A.	
	Examiner	Art Unit	
	Padmashri Ponnaluri	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 January 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-28* is/are pending in the application.

4a) Of the above claim(s) *3* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-2, 4-28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☒ Certified copies of the priority documents have been received in Application No. 08/989,195.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's election without traverse of the following species election a) polyclonal T cells isolated from a site of cytotoxic T cell infiltration as species of cytotoxic T cells; b) polystyrene resin as species of support; c) SEQ ID NO. 1 as a single species of the structural motif; d) inert molecule tag that can be decoded by gas chromatography as coding molecule; e) foster antigen presenting cell as species of antigen presenting means; f) chromium release by target cells as species of method of detecting T cell activation; g) acid cleavable linker as species of releasable linker, filed in the response filed on 1/16/04 is acknowledged.

2. Claim 3 is withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected species invention, there being no allowable generic or linking claim. Election was made **without** traverse in Paper filed on 1/16/04.

3. Claims 1-2, and 4-28 are currently being examined in this application.

Priority

4. This application is a continuation of 08/989,195, which is a continuation of PCT/US97/04479; which claims priority to 60/013,706.

5. Applicants are requested to update the current status of parent applications in the specification page 1.

Information Disclosure Statement

6. The information disclosure statement filed on 1/9/02 fails to comply with 37 CFR 1.98(a)(1), which requires a list (PTO 1449 is missing) of all patents, publications, or other information submitted for consideration by the Office. It has been placed in the application file, but the information referred to therein has not been considered.

Claim Rejections - 35 USC § 112

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 1-2, 4-28 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is vague and indefinite by reciting 'structure of the molecule can be determined...'. The recitation of 'can' is indefinite, applicants are requested to amend the claim.

Claim 1 recites 'a portion of the releasable linker...', and ' a portion of the molecule..'. Applicants are requested to clarify what does applicants mean by a portion of the releasable linker. Does applicants mean cleaving releasable linker from the solid phase supports. And 'a portion of the molecule' is indefinite. It is not clear whether applicants mean the molecule is portioned into different parts, and a portion of it is released (i.e., a peptide with 100 aa length, from that a 50 aa length peptide is released) or applicants mean molecules from some of the solid supports are released. Applicants are requested to amend the claim.

Claim 1 recites 'cleaving .. a portion of the molecule' in step b). It is not clear whether the step b) cleaving is done after contacting the library of molecules with cytotoxic T cells. Applicants are requested to amend the claim to recite the correct order of the claims.

Claim 8 recites 'library of molecules is selected from the group consisting of LxxxxxxV(SEQ ID NO: 1) ..... (L, I)xxxxx(H, K) (SEQ ID NO: 9)....' Applicants are requested to amend the claim as "...library of molecules is selected from the group consisting of LxxxxxxV(SEQ ID NO: 1) .....**and** (L, I)xxxxx(H, K) (SEQ ID NO: 9)...."

Claim 9 is vague and indefinite by reciting 'a limited number of representative amino acid residues are incorporated in the peptides of the library.' It is not clear what does applicants mean by limited number representative amino acid residues. The term 'limited' is a relative term. Applicants are requested to amend the claim.

Claim 24 is vague and indefinite by reciting 'the structure of the molecule is determined after isolating more than one candidate solid phase support...', it is not clear what does

applicants mean by candidate solid phase support. Applicants are requested to clarify what are candidate solid supports in the instant claimed invention.

Claim 25 is vague and indefinite by reciting 'structure of the molecule can be determined...'. The recitation of 'can' is indefinite, applicants are requested to amend the claim.

Claim 25 recites 'a portion of the releasable linker...', and ' a portion of the molecule..'. Applicants are requested to clarify what does applicants mean by a portion of the releasable linker. Does applicants mean cleaving releasable linker from the solid phase supports. And 'a portion of the molecule' is indefinite. It is not clear whether applicants mean the molecule is portioned into different parts, and a portion of it is released (i.e., a peptide with 100 aa length, from that a 50 aa length peptide is released) or applicants mean molecules from some of the solid supports are released. Applicants are requested to amend the claim.

Claim 26 is vague and indefinite by reciting 'structure of the molecule can be determined...'. The recitation of 'can' is indefinite, applicants are requested to amend the claim.

Claim 26 recites 'a portion of the releasable linker...', and ' a portion of the molecule..'. Applicants are requested to clarify what does applicants mean by a portion of the releasable linker. Does applicants mean cleaving releasable linker from the solid phase supports. And 'a portion of the molecule' is indefinite. It is not clear whether applicants mean the molecule is portioned into different parts, and a portion of it is released (i.e., a peptide with 100 aa length, from that a 50 aa length peptide is released) or applicants mean molecules from some of the solid supports are released. Applicants are requested to amend the claim.

Claim Rejections - 35 USC § 103

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

10. Claims 1-2, 4-7, 9-17, 19-28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Van der Zee et al (European Immunology, 1989., vol. 19, pages 43-47) and Lam et al (US Patent 5,510,240).

Van der Zee et al teach a method for efficient mapping and characterization of a T cell epitope by the simultaneous synthesis of multiple peptides. Van der Zee uses Pepscan method to synthesize T cell epitopes, according to the method small amounts of several hundreds of. peptides are synthesized on activated polyethylene rods (solid supports of the instant claims) arrayed in a microtiter plate, after the synthesis and deprotection the peptides (refers to the library of molecules attached to solid phase supports) remain attached to the rods for subsequent analysis of their reactivity with antibodies. Van der Zee teaches that for identification and characterization of T cell epitopes, the peptides must be detached from the solid support for screening assay. Van der Zee et al teach that T cell clones A2b and A2c are used in T cell stimulatory activity assay. The reference teaches that the T cell clone are incubated with peptides which are released from the rods, in presence of irradiated syngenic thymocytes APC, and the stimulatory indices are determined using the ^{3}H-thymidine incorporation. The reference also discloses the sequence of the epitope peptides is determined, and substituted peptides are

prepared by single amino acid substitutions, insertions and deletion and the analogs of the peptides are tested for activity using the same T cell clones. The reference teaches that Pepscan method was also used to prepare a large number of epitope analogs having replacements, deletions, insertions of the residue in the nonpeptide that contain the epitope. Van der Zee et al teach that a heptapepide synthesized by the pepscan method fully stimulated T cell clones. The reference teaches that the activity of the peptides released from the supports are compared. The reference teaches that determination of the essential residue of the epitope by synthesis of variants and capered or determined the T cell stimulations by the variants.

The claimed invention differs from the prior art teachings by reciting using acid releasable linkers and cleaving a portion of the linker molecules such that a portion of the molecule is released. Van der Zee et al do not teach cleaving only a portion of the linkers such that a portion of the molecule is released. However, Lam et al teach methods of screening a peptide library. Lam et al teach synthesis of peptides on solid phase supports using selectively cleavable linkers (refers to the releasable linkers of the instant claims) to allow sequential cleaving the compounds from a single bead (e.g., see column 16). The reference teaches that Van der Zee et al use aqueous formic acid (refers to acid cleaving or releasing agent of the instant claims) as cleaving agent in the method of characterization of T-cell determinants. The reference teaches that the library of bio-oligomers are attached to beads with selectively cleavable linkers such that a fraction of bio-oligomers are released during each step of cleaving and this sequential release of bio-oligomers can result fro use of two different cleavable linkers or by limiting the cleavage agent or controlled irradiation (e.g., see column 22). Beads from wells demonstrating biological activity are isolated and attached bio-oligomer is sequenced. Lam et al teach that in

the disclosed screening method only small number of beads are removed during each screening step, the majority of the beads remain in the pool, therefore the random bio-oligomer can be reused multiple times.

Thus, it would have been obvious to one skilled in the art at the time the invention was made to use selectively cleavable linkers to attach peptides to beads taught by Lam et al in the method of Van der Zee et al with the expectation of identifying T cell epitopes from the library and synthesizing variants of the epitope. Because Lam et al teach advantages of the use of cleavable linkers, such that only a fraction of peptides are cleaved from the beads to identify the T cell epitopes taught by Van der Zee et al and still have peptides attached to the beads which would be useful in structure analysis methods and Van der Zee et al teach methods of synthesis of T cell epitopes on solid phase supports and methods for identifying the t cell epitope using T cell clones and APC. Van der Zee et al teach that the positive peptides from the library are sequenced and using the sequence data of the positive peptides new variant peptides are made and these variants are tested for T cell stimulation. Thus, one skilled in the art at the time the invention was made, motivated to use the methods of Lam et al in the methods of Van der Zee with the expectation of identifying T cell epitopes and determine the structure of the epitopes and use the information in synthesis of T cell epitope variants which would be useful as therapeutics or in diagnosis.

11. Claims 1-2, 4-17, 19-28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Van der Zee et al (European Journal of Immunology. 1989, vol. 19, pages 43-47) and Lam et al (US Patent 5,510,240) as applied to claims 1-2, 4-7, 9-17, 19-28 above, and further in view of Engelhard (Current Opinion in Immunology. 1994, vol. 6, pages 13-23).

Van der Zee et al and Lam et al have been discussed supra.

The combined teachings of Van der Zee et al and Lam et al fail to teach the structural Motif (i.e., SEQ ID NO: 1 of the instant claim 8) contained in the library of molecules. However, Engelhard teaches structure of peptides associated with MHC class I molecules. The reference teaches the recent progress in understanding the structure of MHC class I molecules and the peptides that they bind has led to a generalized model for the peptide binding and an understanding of allele specificity. Predictions on the basis of motifs and new techniques for peptides analysis have recently resulted in the identification of several peptides that comprise peptide epitopes for antigen-specific T cells. The reference teaches that eh ability of individual MHC isoforms to bind diverse arrays pf peptides is based on specific interactions involving into six subsites or pockets located within the deep cleft of on the top surface of the class I molecule, and the predominant length of peptides associated with most class I molecules analyzed to date is nine residues (e.g., see table 1). The reference teaches peptides which have leucine (L) and valine (V) at the terminal and six other amino acids in between (refers to instant claim 8, SEQ ID NO: 1). The reference also teaches that the molecular cloning techniques such as cDNA library are useful to identify epitopes recognized in to database of peptides associated with many different class I MHC molecules, and the general principles that govern their binding, combined with molecular modeling will allow peptide-MHC interactions to be understood and predicted with greater certainty and use of the existing motif information has also led to the identification of several new epitopes recognized by specific CTLs.

Thus, it would have been obvious to one skilled in the art at the time the invention was made to use the motifs disclosed by Engelhard et al in the methods of Van der Zee et al, and Lam

et al with the expectation of obtaining new T cell epitopes which would bind higher affinity. And using the methods of Van der Zee et al and Lam et al to synthesize a larger number of peptides simultaneously and screen for higher affinity T cell epitope and determining the structure of the peptide.

12. Claims 1-2, 4-7, 9-28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Van der Zee et al as applied to claims 1-2, 4-7, 9-17, 19-28 above, and further in view of Melief et al (US Patent 5,554,724).

Van der Zee et al and Lam et al have been discussed supra.

The combined teachings of Van der Zee et al and Lam et al fail to teach that the foster antigen presenting cell is from the cell line 174xCEM.T2. However, Melief et al teach isolated tumor antigen precursor MAGE-2 derived peptides, and uses thereof. The reference teaches that these peptides bind with HLA-A2 molecule, thus presenting the complexes which provoke CTL production. The reference teaches 174xCEM.T2 line which express empty and unstable HLA-A2.1 molecules that can be stabilized when a peptide is binding to the peptide presenting grove of these molecules. The reference teaches that only limited number of peptide bind to HLA-A2.1 with high affinity and which will be recognized by CTLs, because CTL recognizes peptides only when they are bound to HLA molecules. Thus, it would have been obvious to one skilled in the art at the time the invention was made to use 174xCEM.T2 cell line disclosed by Melief et al in the method of Van der Zee et al and Lam et al with the expectation of identifying high affinity T cell epitopes and with the expectation of using them as immunotherapeutics.

Conclusion

13. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Padmashri Ponnaluri whose telephone number is 571-272-0809. The examiner is on Increased Flex Schedule and can normally be reached on Monday through Friday between 7 AM and 3.30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on 571-272-0811. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Padmashri Ponnaluri
Primary Examiner
Art Unit 1639

Pp
16 April 2004

PADMASHRI PONNALURI
PRIMARY EXAMINER